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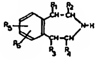
(54) NEW PROCESSES FOR THE PRODUCTION OF BENZAZEPINE DERIVATIVES

(71) We, J. R. GEIGY A.G., a Body Corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns a new process for the production of tetrahydro-azepine derivatives and their addition salts with inorganic or organic acids.

Up to the present, no economically workable process for the production of 2,3,4,5-tetrahydro - 1H - 3 - benzazepines which, in the azepine ring, have no substituents or, e.g. have hydrocarbon radicals as C-substituents, have previously been disclosed. Although the unsubstituted 2,3,4,5-tetrahydro-1H-3-benzazepine is obtained in good purity by high pressure hydrogenation of 1,2-phenyldiacetonitrile in ammonia using a nickel catalyst [P. Ruggli et al., Helv. Chi., Acta. *18*, 1394 (1935) and *20*, 925—927 (1937)] the yields obtained are low. The application of this process to 2,3,4,5-tetrahydro-1H-3-benzazepines having hydrocarbon radicals as C-substituents in the azepine ring has not been disclosed and would be uneconomical. In addition, the starting materials required therefor would be extraordinarily difficult to obtain. However, as such tetrahydro-3-benzazepines have become of considerable importance in the last few years, it became necessary to develop a simple and economically workable process for the production of these and similar compounds.

According to the present invention 2,3,4,5-tetrahydro - 1H - 3 - benzazepines of general formula I



(I)

wherein

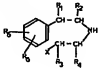
R_1 and R_2, independently of each other, represent a hydrogen atom, an alkyl group containing maximally 6 carbon atoms, a cycloalkyl group having from 3 to 7 carbon atoms as ring members or a phenyl group optionally substituted by a chlorine, fluorine or bromine atom and/or by an alkyl group containing maximally 6 carbon atoms,

R_3 and R_4 have the meanings given above for R_1 and R_2 or together, they represent a trimethylene or tetramethylene radical,

R_5, represents a hydrogen or a halogen atom, and

R_6, represents a hydrogen, chlorine, fluorine or bromine atom, an alkyl group containing maximally 6 carbon atoms or a trifluoro methyl group,

provided that no more than two of the symbols R_1, R_2, R_3 and R_4 may simultaneously represent a cycloalkyl group or an optionally substituted phenyl group, are produced by treating a phenylethylamine derivative of general formula II



(II)

[*Price 5s. 0d. (25p)*]

wherein the symbols

R_1 to R_6 have the meanings given above, and

X represents a fluorine, chlorine or bromine atom, or an addition salt of such a compound with an inorganic or organic acid, with a Lewis acid at a temperature of from 100 to 300° C substantially isolating the end product formed of formula I, and if desired converting the compound of general formula I so obtained into its acid addition salt with an inorganic or organic acid.

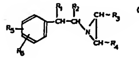
As halogen, X is preferably chlorine or bromine.

Lewis acids which can be used in the process according to the invention are, e.g.: antimony-(V)-chloride, iron-(III)-chloride, tellurium-(II)-chloride, stannic-(IV)-chloride, titanium - (IV) - chloride, tellurium - (IV)-chloride, bismuth-(III)-chloride, zinc chloride and, in particular, aluminium chloride, as well as corresponding bromides and iodides, also borontrifluoride or borontrichloride, hydrogen fluoride, sulphuric acid, phosphorus pentoxide or polyphosphoric acid. The Lewis acid is usually added in an amount of 0.5—5 mol %, preferably 1—1.5 mol % to the reaction mixture. The temperatures for reaction with the Lewis acid are from 100° to 300° C, and preferably from 150° to 250° C.

The tetrahydro-benzazepines are isolated by adding a base to the reaction mixture, preferably an inorganic base, e.g. an alkali hydroxide such as sodium hydroxide, potassium hydroxide, or an alkaline earth oxide.

The reaction of a compound of general formula II and a Lewis acid does not require a solvent or diluent though for example nitromethane, nitrobenzene and *o*-dichlorobenzene may be employed as such.

Starting materials of general formula II may be obtained e.g. by adding a hydrogen halide in a known manner to an aziridine derivative of general formula III



(III)

wherein R_1 to R_6 have the meanings given in formula I.

Compounds of general formula III can be obtained in their turn according to the British Patent Specification No. 692,368 and according to Herbert Bestian, Ann. 566, p. 238—239, by adding alkylene imines to styrenes in the presence of an alkali metal.

The process according to the invention enables 2,3,4,5-tetrahydro-1H-3-benzazepines to be produced in good yield and high purity in a simple and economical way. It has a particular advantage in that the starting materials necessary are easily accesible.

Some of the 2,3,4,5 - tetrahydro - 1H-3-benzazepines which can be produced according to the invention are known (P. Ruggli et al. loc. cit). Both the known and the new compounds of general formula I are very important intermediates for the production of pharmaceuticals.

Compounds of general formula I are used e.g. as intermediate products for the production of N-guanidinoalkyl derivatives which have antihypertensive properties, and the unsubstituted 2,3,4,5 - tetrahydro - 1H - 3-benzazepine compound is used as intermediate for the production of arylsulphonyl ureas having a hypoglycaemic action (oral antidiabetics).

The hitherto unknown 7-chloro-2,3,4,5-tetrahydro - 1H - 3 - benzazepine and the salts thereof, which are embraced by general formula I, have an anorexigenic action on oral or parenteral administration.

If desired, the 2,3,4,5 - tetrahydro - 1H-benzapines obtained by the process according to the invention, may be converted into their addition salts in the usual manner with inorganic or organic acids. For example, the acid desired as salt component or a solution thereof is added to a solution of 7-chloro-2,3,4,5 - tetrahydro - 1H - 3 - benzazepine in an organic solvent. Preferably, organic solvents in which the salt has a low solubility are chosen so that the salt can be isolated by filtration. Such solvents are, e.g. acetone, methylethyl ketone, acetone/ethanol, methanol/diethyl ether, ethanol/diethyl ether or diethyl ether.

Instead of the free base, a pharmaceutically acceptable acid addition salt can be used in the preparation of medicaments, i.e. salts with those acids the anions of which are non-toxic in the normal dosages. In addition it is advantageous if the salts to be used as medicaments crystallise well and are not or are only slightly hygroscopic. For example, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, β-hydroxyethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid and embonic acid can be used for the salt formation with 7 - chloro - 2,3,4,5 - tetrahydro - 1H - 3-benzazepine.

The new active substances may be administered orally, rectally or parenterally, The daily dosages of the free bases or of pharmaceutically acceptable salts thereof vary

between 25 and 200 mg for adult patients. Suitable dosage units such as dragées (sugar coated tablets), tablets, suppositories or ampoules, preferably contain 5—50 mg of the active substance according to the invention of a pharmaceutically acceptable salt thereof.

Dosage units for oral administration preferably contain between 1—90% of 7-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine or a pharmaceutically acceptable salt thereof as active substance. They may be produced by combining the active substance with, e.g. solid, pulverulent carriers such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants such as magnesium or calcium stearate or polyethylene glycols, to form tablets or dragée cores. The latter are coated, e.g. with concentrated sugar solutions which can also contain, e.g. gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in easily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g. to distinguish between varying dosages of active substance.

Other suitable dosage units for oral administration are hard gelatine capsules and also soft closed capsules made of gelatine and a softer such as glycerin. The hard gelatine capsules preferably contain the active substance as a granulate, e.g. in admixture with fillers such as maize starch and/or lubricants such as talcum or magnesium stearate and, optionally, stabilisers such as sodium metabisulphite ($Na_2S_2O_5$) or ascorbic acid. In soft capsules, the active substance is preferably dissolved or suspended in suitable liquids such as liquid polyethylene glycols, to which stabilisers can also be added.

Examples of dosage units for rectal administration are suppositories which consist of a combination of the active substance or a suitable salt thereof with a fatty foundation, or also gelatine rectal capsules which contain a combination of the active substance or a suitable salt thereof with polyethylene glycols.

Ampoules for parenteral, particularly intramuscular administration, preferably contain a water soluble salt of the active substance in a concentration of, preferably, 0.5—5%, in aqueous solution, optionally together with suitable stabilisers and buffer substances.

The following prescriptions further illustrate the production of tablets and dragées:

a) 250 g of 7-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride are mixed with 175.80 g of lactose and 169.70 g of potato starch, the mixture is moistened with an alcoholic solution of 10 g of stearic acid and granulated through a sieve. After drying, 160 g of potato starch, 200 g of talcum, 2.50 g of magnesium stearate and 32 g of colloidal silicon dioxide are mixed in and the mixture is pressed into 10,000 tablets each weighing 100 mg and containing 25 mg of active substance. If desired, the tablets can be grooved for better adaptation of the dosage.

b) A granulate is produced from 250 g of 7-chloro - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride, 175.90 g of lactose and the alcoholic solution of 10 g of stearic acid. After drying, the granulate is mixed with 56.60 g of colloidal silicon dioxide, 165 g of talcum, 20 g of potato starch and 2.50 g of magnesium stearate and the mixture is pressed into 10,000 dragée cores. These are then coated with a concentrated syrup made from 502.28 g of crystallised saccharose, 6 g of shellac, 10 g of gum arabic, 0.22 g of dyestuff and 1.5 g of titanium dioxide and dried. The dragées obtained each weigh 120 mg and contain 25 mg of active substance.

The following examples illustrate the production of compounds of general formula I according to the process of the present invention. The temperatures are given in degrees Centigrade.

EXAMPLE 1.

a) 389 g of N-[(2-chloroethyl)-phenylethylamine]-hydrochloride are finely pulverised, mixed with 470 g of aluminium chloride and the mixture is slowly heated in an oil bath to 180° (bath temperature) and kept at this temperature for 12 hours. After cooling to about 100°, the melt is poured onto ice. 2000 ml of concentrated, aqueous sodium hydroxide solution are added to this stirred solution and, after the precipitate has dissolved, it is extracted with ether. The ethereal solution is dried over magnesium sulphate/potassium carbonate, the drying agent is filtered off and the ether is evaporated. The residue is fractionated in vacuo. The 2,3,4,5-tetrahydro-1H-3-benzazepine obtained boils at 65°/0.1 Torr (M.P. 10°); n_D^{20}=1.565.

The hydrochloride melts at 248—250°.

The starting material N-[(2-chloroethyl)-phenylethylamine]-hydrochloride is obtained as follows:

b) 900 ml of styrene are added dropwise while stirring to 745 ml of ethylene imine and 9 g of metallic sodium; 100 ml of the styrene are added quickly whilst the remaining 800 ml are added so that the temperature of the reaction mixture is maintained at a temperature of from 40—45°. On completion of the dropwise addition, the mixture is stirred overnight at room temperature. The unreacted sodium is removed by mechanical means and the excess ethylene imine is distilled off under reduced pressure. The residue is fractionated in vacuo. The 1-phenyl-2-(N-aziridinyl)-ethane so obtained boils at 48°/0.1 Torr; n_D^{20}=1.5205.

c) 500 ml of methanol are stirred and, saturated with hydrogen chloride in an ice bath. 100 g of 1-phenyl-2-(N-aziridinyl)-

ethane dissolved in 100 ml of methanol are added dropwise at a temperature of 10—15°. The solution is then evaporated to dryness in vacuo and the residue is dried in a drying chamber. The N - [(2 - chloroethyl)-phenylethyl-amine]-hydrochloride formed melts, when recrystallised from ethanol/glacial acetic acid, at 188—190°.

EXAMPLE 2.

a) 234 g of N-(2-chloroethyl)-β-methyl-phenylethylamine hydrochloride are heated for 15 hours at 170° with 200 g of aluminium chloride. The reaction mixture is poured onto ice, while still hot, and the mixture is made alkaline with 2000 ml of 30% aqueous sodium hydroxide solution. A brown oil separates. The alkaline solution is extracted several times with ether. The combined extracts are dried over potassium carbonate/magnesium sulphate, the ether is distilled off and the oily residue is fractionated. The 5-methyl - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine so obtained boils at 72° under 0.6 Torr (n_D^{20}=1.5580).

b) 281 g of phenyl-1-methyl-2-(1'-aziridinyl)-ethane, (produced according to example 1b) from α-methyl styrene and ethylene imine) are added to 800 ml of ethyl alcohol which has been saturated with hydrogen chloride. The temperature of the reaction mixture rises to 30° and a crystalline precipitate is formed. The precipitation is completed by the addition of diethyl ether. The precipitate is filtered off and washed several times with ether. The N-[(2 - chloroethyl) - β - methyl - phenylethyl-amine]-hydrochloride formed melts at 178—180°.

EXAMPLE 3.

a) 120 g of N-[(2-chloroethyl)-p-chloro-phenylethylamine]-hydrochloride are finely pulverised, the powder is mixed with 133 g of aluminium chloride, the mixture is slowly heated in an oil bath while stirring to a temperature of 170—180° (bath temperature) and then kept for 12 hours at this temperature. After cooling to 100°, the melt is poured onto ice. 2.5 litres of concentrated aqueous sodium hydroxide solution are then added to the solution formed while stirring and, after the precipitate has dissolved, the solution is extracted with ether. The ethereal solution is dried over magnesium sulphate/potassium carbonate and concentrated. The residue is fractionated in vacuo. The 7-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine obtained boils at 110—115°/0.1 Torr; n_D^{20}=1.5765.

When recrystallised from acetonitrile, the hydrochloride melts at 171—173°.

The starting substance, N-[(2-chloroethyl)-p-chlorophenylethylamine]-hydrochloride, is produced as follows:

b) 138 g of freshly distilled 4-chlorostyrene are added dropwise to 200 g of dry ethylene imine and 5 g of metallic sodium, the addition being made while stirring; 30 ml of the styrene are quickly dropped in whilst the remainder is so added that the temperature of the reaction mixture does nor exceed 40°. On completion of the dropwise addition, the mixture is stirred overnight at room temperature. Any unreacted sodium is removed by mechanical means and the excess ethylene imine is distilled of under reduced pressure. The residue is fractionated under high vacuum. The 1 - (p - chloro - phenylethyl)-aziridine obtained boils at 93°/0.7 Torr; n_D^{20}=1.5357.

c) 500 ml of methanol are stirred in an ice bath and saturated with hydrogen chloride. 140 g of the aziridine obtained according to b) in 100 ml of methanol are added dropwise at a temperature of 10—15°. The solution is then concentrated to dryness and the residue is dried in vacuo at 60°. The N-[(2-chloro-ethyl) - p - chloro - phenylethylamine]-hydrochloride formed melts, when recrystallised from acetonitrile, at 189—191°.

EXAMPLE 4.

14 g of polyphosphoric acid are heated to 150° and 1 g of N-[(β-chloro-β-phenylethyl)-phenylethylamine]-hydrochloride is added in portions. On completion of the addition, the whole is kept for half an hour at 150°. The clear solution is poured onto 15 g of ice whereupon a precipitate is formed. The mixture is made alkaline with 30% NaOH while cooling and the oil which separates is taken up in methylene chloride. After distilling off the methylene chloride, the 1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine is distilled under high vacuum at 140—150°.

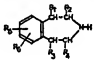
EXAMPLE 5.

The phenylethylamine-hydrochlorides listed in the first column of the following table are obtained in a manner analogous to that described in examples 1 to 4 from aziridine derivatives according to the British Patent Specification No. 692,368 and according to Herbert Bestian *Ann*, 566, p. 238—239. The 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine derivatives listed in the third column are obtained by the process according to the invention:

phenylethylamine hydrochloride	M.P.	2,3,4,5-tetrahydro-1H-3-benzazepine	physical data
N-[(1'-methyl-2'-chloro-ethyl)-phenylethylamine]-hydrochloride	160—165°	2-methyl-2,3,4,5-tetrahydro-1H-3-benzazapine	B.P.60°/0.2 Torr
N-[(β-chloro-β-phenylethyl)-phenylethylamine] hydrochloride	168—170°	1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine	B.P. 140—150°/ 0.01 Torr n_D^{20}=1.4670
N-[(2-chlorocyclohexyl)-phenylethylamine]-hydro-chloride	165—167°	2,3,4,4a,5,6,7,11b-octahydro-1H-dibenz[b,d]azepine	B.P. 150—155°/ 0.01 Torr
N-[(2'-chloroethyl)-α-methylphenylethylamine]-hydrochloride	149—151°	4-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine	B.P. 64°/0.2 Torr, n_D^{20}=1.5507
N-[(2'-chloroethyl)-β-methyl-4-isopropylphenyl-ethylamine]-hydrochloride	184—186°	5-methyl-8-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine	B.P. 71—72°/ 0.2 Torr n_D^{20}=1.5554

WHAT WE CLAIM IS:—

1. Process for the production of 2,3,4,5-tetrahydro-1H-3-benzazepines and derivatives thereof having the general formula I



(I)

wherein

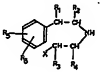
R_1 and R_2, independently of each other, represent a hydrogen atom, an alkyl group containing maximally 6 carbon atoms, a cycloalkyl group having from 3 to 7 carbon atoms as ring members or a phenyl group optionally substituted by a chlorine, fluorine or bromine atom and/or by an alkyl group containing maximally 6 carbon atoms,

R_3 and R_4 have the meanings given above for R_1 and R_2 or together, they represent a trimethylene or tetramethylene radical,

R_5, represents a hydrogen or a halogen atom, and

R_6, represents a hydrogen, chlorine, fluorine or bromine atom, an alkyl group containing maximally 6 carbon atoms or a trifluoro methyl group

provided that no more than two of the symbols R_1, R_2, R_3 and R_4 may simultaneously represent a cycloalkyl group or an optionally substituted phenyl group, which process comprises treating a correspondingly substituted phenethylamine derivative having the general formula II



(II)

wherein

X represents a chlorine, fluorine or bromine atom, or an acid addition salt thereof, with a Lewis acid at a temperature of from 100 to 300° C and substantially isolating the desired 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine or derivative thereof.

2. Process as claimed in claim 1 wherein X represents a chlorine or bromine atom.

3. Process as claimed in claim 1 or 2 wherein the Lewis acid is aluminium chloride.

4. Process as claimed in any one of claims 1 to 3 wherein the Lewis acid is present during the reaction in an amount of from 0.5 to 5.0 mol % of the reaction mixture.

5. Process as claimed in claim 4 wherein the Lewis acid is present during the reaction in an amount of from 1.0 to 1.5 mol % of the reaction mixture.

6. Process as claimed in any one of claims 1 to 5 wherein the reaction is effected at a temperature of from 150 to 250° C.

7. Process as claimed in any one of claims 1 to 6 wherein the 2,3,4,5-tetrahydro-1H-3-benzazepine, or derivative thereof, thus obtained is converted into a pharmaceutically acceptable acid addition salt thereof.

8. Process as claimed in any one of claims 1 to 7 wherein one of the symbols R_5 or R_6 represents a halogen atom.

9. Process as claimed in claim 8 wherein the halogen atom is a chlorine atom.

10. Process as defined in claim 1 substantially as hereinbefore described with reference to any one of the examples 1, 2 and 5.

11. Process as defined in claim 1 substantially as hereinbefore described with reference to example 3.

12. Process as defined in claim 1 substantially as hereinbefore described with reference to example 4.

13. 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine and derivatives thereof having the general formula I and the pharmaceutically acceptable acid addition salts thereof whenever prepared by a process as claimed in any one of the foregoing claims 1 to 9.

14. 7 - Chloro - 2,3,4,5 - tetrahydro - 1H-3-benzazepine.

15. The pharmaceutically acceptable acid addition salts of 7-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine.

16. 7 - Chloro - 2,3,4,5 - tetrahydro - 1H-3-benzazepine hydrochloride.

17. Process for the production of 7-chloro-2,3,4,5 - tetrahydro - 1H - 3 - benzazepine comprising treating a substituted phenylethylamine of the formula II laid out in claim 1 in which R_1, R_2, R_3, R_4 and R_5 represent hydrogen and R_6 represents chlorine in the 7-position; or an acid addition salt thereof with a Lewis acid at a temperature of from 100° to 300° C and isolating the benzazepine so formed.

18. Pharmaceutical composition comprising 7 - chloro - 2,3,4,5 - tetrahydro - 1H - 3-benzazepine or a pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier thereof.

19. Pharmaceutical composition comprising a compound as claimed in claim 13 together with a pharmaceutically acceptable diluent or carrier therefore.

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